

Remarks/Arguments

A. Summary Of the Claims

Claims 6 and 35 were pending at the time the Action was mailed. No claims are amended, cancelled, or added herein. Thus, claims 6 and 35 remain pending.

B. The Obviousness Rejection Is Overcome

Claims 6 and 35 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Application No. 2003/0124184 by Mezaache in view of WO 97/48384 and Orifer F Prenatal Vitamin Supplement (September 25, 1996) ("Orifer F"). The Action asserts that it would be obvious to combine features of Orifer F with the teachings of Mezaache regarding embossed tablets that are said to comprise the presently claimed active ingredients and the teachings of WO 97/48384 regarding imprinting markings on dosage forms to arrive at the presently claimed invention. Action, page 2.

Applicant respectfully traverses. Not only is Mezaache not prior art with respect to the claimed invention, but an analysis of the *Graham* factors does not lead to a conclusion of obviousness. Furthermore, even if a *prima facie* case of obviousness has been established, which Applicant does not concede, objective evidence of nonobviousness demonstrates that the rejection is improper. Each of these points alone supports the withdrawal of the obviousness rejection.

1. Mezaache Is Not Prior Art

Mezaache is not prior art with respect to the claimed invention. Mezaache is a Continuation-in-Part (CIP) application of U.S. Serial No. 09/179,926 filed on October 27, 1998 (copy enclosed as Appendix 1). The '926 application, abandoned in March of 2003, never published. The CIP, filed on June 21, 2002, published on July 3, 2003. Mezaache was therefore

published after the filing date of the present application (*i.e.*, after July 1, 2003). Thus, this document may not be cited in a 35 U.S.C. §§ 103(a)/102(a) or (b) rejection.

Regarding a possible rejection under 35 U.S.C. § 102(e), Applicant encloses a Declaration under 37 C.F.R. § 1.131 by one of the inventors, Eric Gervais. Mr. Gervais explains that the claimed invention was conceived and reduced to practice prior to the filing date of Mezaache (June 21, 2002). *See* Declaration, para. 6. As such, Mezaache is not prior art with respect to § 102(e). Moreover, the '926 parent application of Mezaache does not contain all of the teachings upon which the Examiner appears to have based his obviousness rejection. Thus, this document cannot serve as anticipatory prior art.

In view of the above, Mezaache may not be relied upon as prior art and as such, the present obviousness rejection is moot. Despite Applicant's showing that Mezaache is not prior art, Applicant provides arguments to establish that any combination of Mezaache, WO 97/48384 and Orifer F does not render the claimed invention obvious.

2. A *Prima Facie* Case of Obviousness Has Not Been Established

As with the previously issued Action, the Examiner appears to have relied on the *Graham* factors to assess obviousness in the present Action. *See* 72 Fed. Reg. 57256, 57527 (October 10, 2007), *citing KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). These factual inquiries include determining the scope and content of the prior art, and ascertaining the differences between the claimed invention and the prior art. However, an analysis of these factors does not establish *prima facie* obviousness. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)). For example, in attempting to provide an apparent reason why the cited art, in combination, renders the claimed invention obvious, the Action relies on impermissible hindsight bias. Moreover, there is no reasonable expectation of success regarding any alleged combination of the cited art.

a. The rejected claims and the scope and content of the cited art

Each rejected claim is drawn to subject matter regarding a pharmaceutical tablet that comprises therapeutically effective amounts of two different active ingredients: doxylamine succinate and pyridoxine hydrochloride. Each claim recites that doxylamine succinate is perceived as causing teratogenicity. Each claim also recites that the tablet comprises a graphical representation of a pregnant woman applied to the tablet surface. The graphical representation is visible to the naked eye in each claim. Claim 6 recites that the tablet is destined for administration to pregnant women.

The scope and content of both WO 97/48384 and Orifer F are explained in Applicant's Response to Office Action dated March 5, 2008 ("the March 2008 Response"), and incorporated herein by reference. Mazaache relates to a composition useful for making oral dosage forms capable of dissolving in the mouth in less than 40 seconds without the need for a conventional super disintegrant and having a friability of less than 1%, wherein the composition includes liquiflash particles and an excipient mass. *See* Abstract and claim 1. The technical problem tackled in Mezaache thus concerns drug delivery, formulation issues and their impact on dissolution rapidity in the mouth as well as tablet physical properties. *See id.*, para. [0002]. Mezaache mentions doxylamine succinate and pyridoxine in one instance: para. [0063].

b. Differences between the rejected claims and the cited art

Differences between the subject matter of the rejected claims and Orifer F are described in the March 2008 Response as well as the differences between the subject matter of the rejected claims and WO 97/48384, which are incorporated herein by reference. Mazaache differs from the rejected claims in the fact that, for example, Mezaache fails to mention pregnancy, pregnant women or graphical representations thereof, teratogenicity, or any active ingredient perceived as

causing teratogenicity. Moreover, Mezaache characterizes doxylamine succinate and pyridoxine as optional ingredients in a composition, and not as active ingredients, as presently claimed.

c. The differences between the rejected claims and the cited art are not obvious differences

In the context of an obviousness rejection, the Supreme Court explained the importance of “identify[ing] a reason” why a skilled artisan would be prompted to arrive at the presently claimed invention. *KSR*, 127 S.Ct. at 1741. The Court noted that there should be an “explicit” analysis regarding “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *Id.* (emphasis added). However, no such reason has been supplied. For example, the reasoning set forth in the Action results from the impermissible use of hindsight bias. Further, there is no reasonable expectation of success that the combination proposed by the Action would work. For at least these reasons, Applicant respectfully requests that the obviousness rejection be withdrawn.

(i) Improper hindsight is used to support the obviousness rejection

Page 2 of the Action provides the reasoning that allegedly supports the obviousness rejection:

It would have been obvious to a person of ordinary skill in the art at the time the invention was made desiring to utilize a graphic design on a drug tablet to indicate prenatal consumption, to use one of MEZAACHE modified with a figure of ORIFER, in order to enhance acceptability & consumption by pregnant women.

(emphasis added). As will be shown, the basis for this reasoning comes from the Applicant’s own disclosure. This is an improper use of hindsight, as explained by *KSR*, 127 S.Ct. at 1742 (warning that caution must be used when basing arguments on *ex post* reasoning).

The presently claimed invention, which is not taught or suggested in the art, is improperly used as a premise to support the obviousness rejection. The present disclosure explains that, due to perceived risks of teratogenicity associated with medications, such as

prescription medications, pregnant women frequently decide to discontinue taking such medications. Specification, paras. [0002]-[0018]. Despite showings of non-teratogenicity of a variety of medications by healthcare professionals and labels to this effect, these perceptions persist and result in pregnant women ceasing medication ingestion. *See id.* at paras. [0010] and [0013]; *see also* Declaration of Gideon Koren, M.D., filed with Applicant's Response dated October 12, 2006 ("the Koren Declaration"), at para. 13.

At the time the present application was filed, there were no known pharmaceutical tablets on which a graphical representation of a pregnant woman was placed, nor was there any suggestion that such a placement would result in the unexpected results observed by the present inventors with respect to compliance. *See, e.g.,* Koren Declaration, para. 11.2 and para. VI on page 4. The presently claimed invention is drawn, in part, to the inventors' discovery that placing a graphical representation of a woman on a pharmaceutical tablet, as presently claimed, has a pronounced clinical effect with respect to patient compliance and teratogen perception. *See id.* at paras. 11.2-14; *Can. J. Clin. Pharmacol.* 14(1) Winter 2007:e10-e16; January 5, 2007, filed with Applicant's Response dated March 5, 2008; and Examples 1 and 2 of the present specification.

Yet, as its premise for the obviousness rejection, the Action uses this very discovery as the "template" by which the cited art is "piece[d] together" to support the obviousness rejection. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). The Action states that one "desiring to utilize a graphic design on a drug tablet to indicate prenatal [sic] consumption" would look to the cited art for ways in which to execute this desire, ***but the desire itself speaks to Applicant's claimed invention*** which recites, in part, "A pharmaceutical tablet... comprising a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity [and] further comprising a graphical representation of a pregnant woman

applied to the tablet surface, said graphical representation being visible to the naked eye.” In other words, the Action appears to assume that the desire to “utilize a graphic design on a drug tablet to indicate prenatal [sic] consumption” was a concept known in the art *before* the present application was filed. Yet none of the cited art teaches or suggests this concept. This assumption leads to impermissible hindsight bias:

To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction—an illogical and inappropriate process by which to determine patentability.

Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570 (Fed. Cir. 1996).

Only with the prior knowledge of the claimed invention can the cited art be combined in a manner that is said to solve the problems set forth by the present application; otherwise, the cited art is unrelated to the present invention. To support the rejection, the Action looks to a combination of art that is said to solve the problem of pregnant women medication compliance and perceptions of medication teratogenicity. However, no one would *look* to this combination of art to solve these problems without *first* using the claimed invention as the premise to combine them. That is, without the present invention as a guide, the combined cited art provides no insight as to how to solve the problems posed by the present disclosure; indeed, the cited art speaks to unrelated problems. This is another instance of improper use of hindsight. *See, e.g., Ex parte Timothy Ford and Stephane Gascon*, Board of Patent Appeals and Interferences, Appeal 2008-1728, decided September 9, 2008 (given the disparity of problems addressed by the cited art and the different solutions they present, any attempt to combine them in a manner proposed by the Examiner is only through the use of hindsight reconstruction from Appellant’s disclosure).

For example, as discussed above, Mezaache concerns drug delivery and formulation issues and their impact on the problem of dissolution rapidity in the mouth. Mezaache solves

this problem by describing a formulation that offers rapid dissolution. Thus, its technical problem and its approach for a solution do not coincide with those of the present invention. Indeed, pregnancy, prenatal medication compliance, and teratogen perception are not mentioned in this reference. A person of skill in the art confronted with a technical problem of lack of compliance among the population of pregnant women due to a high perception of teratogenic risk of some medicaments despite extensive proof to the contrary would not, without impermissible hindsight and the benefit of the present specification, have even considered the teachings by Mezaache. Moreover, Mezaache's lack of direction with respect to combining doxylamine succinate and pyridoxyl hydrochloride as active ingredients further shows that this reference does not speak to the problems solved by the presently claimed invention.

WO 97/48384 is similar in this regard, as this reference only speaks to solving the problems associated with marking the surface of solid rapidly disintegrating dosage forms. WO 97/48384, Abstract. This problem is solved using non-contact marking techniques such as laser imprinting and ink-jet printing. *Id.* Nothing in WO 97/48384 teaches or suggests imprinting any pregnancy-friendly indicia on any pharmaceutical tablet. As discussed in the March 2008 Response, the examples taught by WO 97/48384 of a mark or text that may be applied to a dosage form surface include "a company logo or name, a product name, a trade mark, or a number indicating the amount of active ingredient in the dosage form." *Id.* at page 2, lines 27-29. These types of marks are merely for identification purposes, such as identifying the source of the dosage form or identifying the amount of an ingredient in the dosage form. Once again, one seeking to solve the problems of pregnant women medication compliance and teratogenic risk would not even look to a reference regarding marking of dosage forms unless such a person first was in possession the idea of the presently claimed invention.

Furthermore, Orifer F does not even teach or suggest the problems addressed by the present invention, as Orifer F merely discloses a representation of a pregnant woman on the packaging of a prenatal vitamin supplement. Nothing in Orifer F teaches or suggests (1) any perception of teratogenicity, much less a perception with respect to doxylamine succinate, as that agent is absent from the Orifer F formulation, or (2) any practical effect of graphical indicia representing a pregnant woman on the packaging.

Conclusion. Not only does the reasoning used to support the obviousness rejection require knowledge of the presently claimed invention as a premise, but the cited art has nothing to do with the problems addressed by the claimed invention, such that the art is otherwise unrelated without knowledge of the claimed invention. Thus, there is no apparent reason to combine these references unless such a person is aware of the present invention. Hindsight bias of this nature cannot be said to properly support an obviousness rejection.

(ii) There is no reasonable expectation of success regarding any combination of the cited art

Even if the references could be combined to arrive at the presently claimed invention, which Applicant does not concede, there is no reasonable expectation of success that such a combination would work. This represents yet another reason that counsels against an obviousness finding. *See* MPEP § 2143.02 (“Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness.”).

An example of the success achieved by the claimed invention lies in the increased patient compliance and reduced perception of teratogenicity associated with pharmaceutical tablets of the claimed invention. *See, e.g.,* Examples 1 and 2 of the present specification; Koren Declaration at paras. 11.2-14; and *Can. J. Clin. Pharmacol.* 14(1) Winter 2007:e10-e16; January 5, 2007, filed with Applicant’s Response dated October 27, 2006. This success is tied to

problems the present application sought to solve, as explained in paragraphs [0002]-[0018] of the present specification.

Since there is no mention or suggestion of either problems with pregnant women medication compliance or the perception of teratogenic risk in the cited references, any possible expectation of success in reducing such perception among pregnant women by combining the references could not lie in such documents. Moreover, such an expectation could not be found in a skilled artisan at the time the application was filed. For example, the specification explains that, despite extensive evidence of safety regarding, for example, DiclectinTM, the perception of teratogenic risk remained and caused compliance problems, even though publications and labels attested to its safety. Specification, paras. [0012]-[0015]. Given these observations, it cannot be said that at the time the invention was made an indicia on a tablet such as that presently claimed would make any difference.

Thus, contrary to the Action's assertion that "enhance[d] acceptability and consumption by pregnant women" would result from a combination of the cited references, the status of knowledge at the time the application was filed suggests that expectations in diminishing the perceptions of medication teratogenicity and increasing medication compliance by pregnant women were low. Nothing in these references or the knowledge available to skilled artisans at the time the application was filed permits a reasonable expectation of success regarding combining the cited references in the manner proposed by the Examiner. This presents yet another reason why the obviousness rejection should be withdrawn.

3. Objective Evidence of Nonobviousness Establishes the Patentability of the Claimed Invention

Even if a *prima facie* case of obviousness has been established, which Applicant does not concede, objective evidence of nonobviousness establishes the patentability of the claimed

invention. See MPEP §§ 2141 and 2145 (secondary considerations of nonobviousness are relevant to the obviousness inquiry).

a. The Action Improperly Dismisses Applicant's Objective Evidence of Nonobviousness

Objective evidence of nonobviousness, such as evidence of commercial success and surprising and unexpected results, may be presented to counter an obviousness rejection. See *KSR*, 127 S.Ct. at 1729 and MPEP §§ 2141 and 2145. In this regard, "Office personnel should consider all rebuttal arguments and evidence presented by applications." MPEP § 2145. The Action conveys that objective evidence presented by Applicant in the March 2008 response was considered by stating the following:

Applicant's arguments filed 3/17/08 have been fully considered but they are not persuasive. Arguments are to the unexpected increased purchase of the embossed tablets. We find that given the art of embossing, the increased awareness & purchase are entirely expected, and it would take little testing to determine what figure would best result in consumption of the tablet of concern, with reasonable expectation of success.

Action, page 8. It appears that the Action has given little weight to the objective evidence offered by Applicant. However, "Office personnel should avoid giving evidence no weight, except in rare circumstances." MPEP § 2145. Moreover, "If the evidence is deemed insufficient to rebut the *prima facie* case of obviousness, Office personnel should specifically set forth the **facts and reasoning** that justify this conclusion. *Id.* (emphasis added). No facts have been supplied by the Action in this regard. For example, the Action provides no facts that speak to any expectation that "increased awareness and purchase" was certain. Thus, the Action improperly dismissed the evidence.

In addition, the reasoning provided by the Action also fails to support the dismissal of the evidence. In particular, the Action appears to imply that commercial success must be *unexpected* commercial success: “the increased awareness and purchase are entirely expected....” However, there is no legal requirement that commercial success must be unexpected, and the Action provides no authority for this proposition. While Eric Gervais explained in his Declaration filed with Applicant’s Response dated October 27, 2006 (“Gervais 2006 Declaration”) that the commercial success was, indeed, surprising, any lack of surprise in this regard does not denigrate the objective evidence of commercial success.

In further regard of the weight to be ascribed to objective evidence, MPEP § 2145 states that “to be entitled to substantial weight, *the applicant should establish a nexus between the rebuttal evidence and the claimed invention*, i.e., objective evidence of nonobviousness must be attributable to the claimed invention.” (emphasis added). Mr. Gervais confirmed that such a nexus exists between the claimed invention and the commercial success he described. *See* Gervais Declaration, paras. 7-19. Accordingly, such evidence should not be easily dismissed.

b. The Action Improperly Dismisses the Surprising and Unexpected Results Associated with the Claimed Invention

In the October 2006 and March 2008 Responses, incorporated herein by reference, Applicant provided arguments and declaratory evidence of the surprising and unexpected results associated with the claimed invention. The present Action provides no comment on these results, except to the extent of improperly giving weight to “unexpected commercial success,” as described above. This presents another reason why Applicant’s objective evidence of nonobviousness was improperly dismissed. *See, e.g.*, MPEP § 2141 (objective evidence of obviousness, such as unexpected results, “*must* be evaluated by Office personnel”) (emphasis added). While Applicant maintains that Applicant’s previous Response was sufficient to

overcome the obviousness rejection, Applicant provides the following comments to further establish the patentability of the claimed invention.

As discussed in the October 2006 Response, incorporated herein by reference, the specification demonstrates the clinically significant and statistically reliable effect of placing a graphical representation of a pregnant woman on the surface of a pharmaceutical tablet, as compared to unmarked tablets. *See, e.g.,* specification, Example 2. The reliability and significance of these results have been extensively confirmed thereafter, as discussed in the Declaration of Dr. Koren and in an article published in the *Canadian Clinical Journal of Pharmacology* in 2007, previously of record and incorporated herein by reference. These results have also been recognized by Health Canada, which approved an amendment to the DiclectinTM product monograph in June 2005, as discussed in the March 2008 Response, incorporated herein by reference.

These results, which are commensurate in scope with the claimed invention, were unexpected as of the date the invention was made. Evidence of unexpectedness is apparent, for example, in the present specification. As mentioned in this Response, the specification, the October 2006 and March 2008 Responses, and the Koren Declaration, there was little expectation at the time the invention was made that a graphical representation of a pregnant woman on a tablet would alter pregnant women's perceptions of teratogenic risk with medications and/or increase pregnant women medication compliance. In particular, this surprising effect of the claimed invention was confirmed in the Declaration by Dr. Koren filed with the October 2006 Response, such as at para. 11.2: "The results reported in the '803 application are unexpected. One having practical knowledge of paediatrics and obstetrics would have expected little or no clinical effect stemming from graphical representations placed on dosage forms." Objective evidence of nonobviousness may include this type of information—

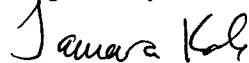
that is, “the state of the art, the level of skill in the art, and the beliefs of those skilled in the art.” MPEP § 2145 (citing *In re Oelrich*, 579 F.2d 86, 91-92 (CCPA 1978) (expert opinions regarding the level of skill in the art are probative of nonobviousness)).

Although the Office Action dated October 5, 2007 discussed the Koren Declaration, Applicant provided further arguments in the March 2008 Response that countered the Action’s dismissal of the Declaration. The present Action makes no reference to this argument, or to Applicant’s additional arguments regarding unexpected results set forth in the March 2008 Response. Again, this is improper and cannot serve to negate Applicant’s showing of surprising and unexpected results. *See* MPEP § 2141.

C. Conclusion

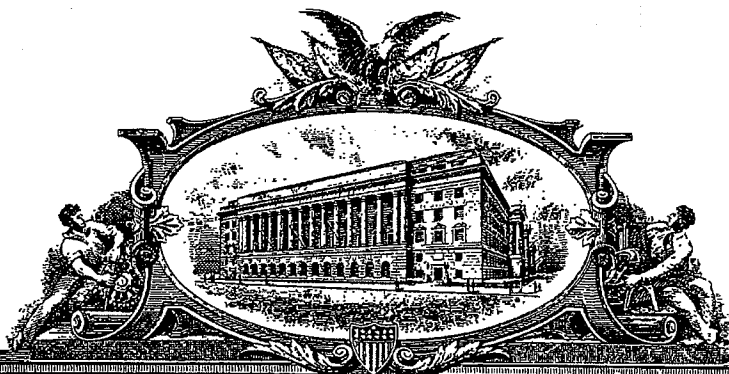
In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-3015 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/179,926

FILING DATE: October 27, 1998

PCT APPLICATION NUMBER: PCT/US99/25071

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By Authority of the
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T. Lawrence

T. LAWRENCE
Certifying Officer

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DOCUMENT**

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COMPLIANCE WITH RULE 17.1(a) OR (b)

APPENDIX 1



PATENT APPLICATION TRANSMITTAL LETTER
(Large Entity)

Docket No.
0051

TO THE ASSISTANT COMMISSIONER FOR PATENTS

Transmits herewith for filing under 35 U.S.C. 111 and 37 C.F.R. 1.53 is the patent application of:

Pradeepkumar P. Sanghvi, Barbara Montwill, Desiree Pereira and Mark R. Herman

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Enclosed are:

1 Certificate of Mailing with Express Mail Mailing Label No. **EH637815243US**
sheets of drawings.

- ☐ A certified copy of a _____ application.
- ☒ Declaration ☒ Signed. ☐ Unsigned.
- ☒ Power of Attorney
- ☐ Information Disclosure Statement
- ☐ Preliminary Amendment
- ☐ Other:

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	10	- 20 =	0	x \$22.00	\$0.00
Indep. Claims	2	- 3 =	0	x \$82.00	\$0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$790.00
TOTAL FILING FEE					\$790.00

- ☐ A check in the amount of _____ to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **06-2232** as described below. A duplicate copy of this sheet is enclosed.
 - ☒ Charge the amount of **\$790.00** as filing fee.
 - ☒ Credit any overpayment.
 - ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
 - ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: *October 25, 1998*

Sandra M. Nolan
Signature

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cc:



Bioaffecting Microparticles

Field of the Invention

The invention deals with microparticles that are produced from compositions
10 containing bio-affecting agents at least one processing aid. The microparticles generally
have very consistent properties and can be readily coated or otherwise processed to yield
dosage forms, or comestible units, having taste-masking and/or controlled release
features. The microparticles are useful in making comestible units for delivery of the
bio-affecting agents via oral, transdermal, or other routes of administration.

Background

The nutritional/therapeutic use of microparticles containing bio-affecting agents,
i.e., drugs, is known. However, the production of microparticles--and especially
microspheres--having highly consistent shape, size and other properties can be
20 problematic. That is, conventional microparticles may suffer from inconsistencies of
shape, size, etc. which can lead to problems during coating, formulating and/or shaping
operations used to produce comestible units.

Applicants' assignee, Fuisz Technologies, owns several patents which deal with
the use of thermoforming techniques to facilitate the production of microparticulates
25 useful in delivery systems for bio-affecting agents. Among these patents are:

U.S. 5,567,439 deals with controlled release dosage forms containing shearform matrix (floss) particles which were ground and employed, along with a glycerol polyethylene glycol behenate in making tablets. See Example 1 therein.

U.S. 5,683,720 refers to discrete microspheres made under liquiflash conditions.

5 The microspheres can be coated and are useful in pharmaceutical products.

In addition, the use of polyethylene glycols (PEG's) in the production of dosage units is known.

U.S. 4,744,976 is concerned with sustained release dosage forms containing a bio-affecting agent in an erodible matrix. The matrix contains a PEG having a molecular weight between 1,000 and 20,000.

U.S. 5,290,569 is directed to the use of PEG's of 400 to 20,000 molecular weight as granulating/binding agents for active agents. The agents are melt granulated with the PEG, then coated with a generally lower melting material.

U.S. 5,403,593 shows melt granulated compositions which employ PEG's as granulating media. Sustained release products are made therewith.

U.S. 5,429,825 deals with a rotomelt granulation process that employs PEG 4000 or PEG 6000 as a binder. See column 5, lines 67-8.

Nonetheless, a need exists for compositions and processes that produce microparticles, especially microspheres, having highly uniform, or consistent, properties.

20 This invention addresses that need.

Summary of the Invention

The invention deals with uniform microparticles comprising (a) at least one bio-affecting agent and (b) at least one processing aid selected from (i) high molecular weight

polyethylene glycols and (ii) polyethylene glycol glyceryl esters. Owing to the presence of one or both of the processing aids described herein, the microparticles containing them have consistent shape and size. That consistency make them readily processable into comestible units or dosage forms via conventional processing techniques. When
5 controlled release agent(s) or taste-masking systems are used in or on the microparticles, these properties are also generally consistent throughout the controlled release and/or taste-masked products produced.

In preferred embodiments, the microparticles are microspheres and the processing aids are used in binary combinations in which each functions as a spheronization aid.

10 Applicants have discovered that certain processing aids, namely one or both of certain PEG's and certain glyceryl esters of same are useful in making microparticles having highly consistent properties.

Detailed Description of the Invention

15 The invention is concerned with bio-affecting microparticles produced from compositions containing a unique combination of ingredients. The composition, the microparticles, their production and comestible units containing them are disclosed.

Unless stated otherwise, all percentages recited herein are weight percentages, based on total composition weight.

20 I. Compositions

The compositions of the invention employ optional excipients with (a) a bio-affecting agent and (b) one or more processing aids.

A. Bio-affecting Agents

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The active ingredients useful herein can be selected from a large group of therapeutic agents. Respective classes include those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics;

5 anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics;

10 antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents;

15 diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral

20 vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others. Active agents which may be

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- used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole;
- 5 ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and
- 10 hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalixin; centriline and its hydrochloride; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylonol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic
- 15 stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine and its hydrochloride; danthron; dexbromopheniramine
- 20 maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride;

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- divalproex and its alkali metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; flurbiprofen; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron and its hydrochloride; griseofulvin; growth hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormone; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine and its hydrochloride; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metoclopramide and its halides/hydrates; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxynol-9; norethindrone and its acetate;

- 

witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate.

Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

Particularly useful active agents are sparingly soluble solid agents whose dissolution and release properties are enhanced by the solubilizing agents used herein.

- 5 These agents include H₂ antagonists, analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), anticholesterolemics, anti-allergy agents, and anti-migraine agents.

Analgesics include aspirin, acetaminophen, acetaminophen plus caffeine, and non-steroidal anti-inflammatory drugs (NSAIDS), *e.g.*, ibuprofen and nimesulide.

- 10 Useful NSAIDs include ibuprofen; diclofenac and its alkali metal salts; fenoprofen and its metal salts; fluriprofen; ketoprofen; naproxen and its alkali metal salts; nimesulide; and piroxicam and its salts.

- H₂-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine,
15 roxatidine, pisatidine and aceroxatidine.

- Useful anti-allergy agents include hydricodone and its tartrates; clemastine and its fumarate; azatadine and its maleate; acetaminophen; hydroxyzine and its pamoate and hydrochloride salts; chlorpheniramine and its maleates and tannates; pseudoephedrine and its sulfates and hydrochlorides; bromopheniramine and its maleate;
20 dextromethorphan and its hydrohalides; loratadine; phenylephrine and its tannates and hydrochlorides; methscopolamine and its nitrates; phenylpropanolamine and its hydrochlorides; codeine and its hydrochloride; codeine and its phosphate; terfenadine; acrivastine; astemizole; cetirizine and its hydrochloride; phenindamine and its tartrate;

tripelennamine and its hydrochloride; cyproheptadine and its hydrochloride; promethazine and its hydrochloride; and pyrilamine and its hydrochlorides and tannates.

Useful antimigraine agents include divalproex and its alkali metal salts; timolol and its maleate; propanolol and its hydrohalides; ergotamine and its tartrate; caffeine; 5 sumatriptan and its succinate; dihydroergotamine, its hydrogenates/mesylates; methsergide and its maleate; isometheptene mucate; and dichloralphenazone.

Another class of drugs which can be used are antiemetics. Useful antiemetics include: meclizine and its hydrochloride; hydroxyzine and its hydrochloride and pamoate; diphenhydramine and its hydrochloride; prochlorperazine and its maleate; 10 benzquinamide and its hydrochloride; granisetron and its hydrochloride; dronabinol; bismuth subsalicylate; promethazine and its hydrochloride; metoclopramide and its halides/hydrates; chlorpromazine; trimethobenzamide and its hydrochloride; thiethylperazine and its maleate; scopolamine; perphenazine; and ondansetron and its hydrochloride.

15 Other active ingredients for use in the present invention include antidiarrheals such as immodium AD, antihistamines, antitussives, decongestants, vitamins, and breath freshners. Also contemplated for use herein are anxiolytics such as Xanax; antipsychotics such as Clozaril and Haldon; antihistamines such as Seldane, Hismanal, Relafen, and Tavist; antiemetics such as Kytril and Cesamet; bronchodilators such as 20 Bentolin, Proventil; antidepressants such as Prozac, Zoloft, and Paxil; antimigranes such as Imigran, ACE-inhibitors such as Vasotec, Capoten and Zestril; Anti-Alzheimers agents such as Nicergoline; and Ca^{++} -Antagonists such as Procardia, Adalat, and Calan.

Among the anticholesterolemics, the statins, *e.g.*, lovastatin, provastatin and the like are notable.

Famotidine and lovastatin are preferred active agents.

Combinations of various types of drugs, as well as combinations of individual
5 drugs, are contemplated.

B. Processing Aids

The processing aids of the invention include high molecular weight polyethylene glycols (PEG's) and/or polyethylene glycol glyceryl esters. When microspheres are made, these materials can be called "spheronization aids."

10 By "high molecular weight polyethylene glycols (PEG)," applicants mean PEG's having molecular weights of about 3,000 to about 8,000. "PEG 4600," having an average molecular weight of about 4400 to 4800, is a preferred material. Mixtures can be used.

In chemical terms, useful PEGs are those molecules having the structural formula $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_m\text{CH}_2\text{OH}$, wherein *m* is the average number of oxyethylene groups.
15 PEG's used for this invention are those in which *m* is from about 0 to about 13.

Useful PEGs are solids. They are discussed on pages 355-361 of the Handbook of Pharmaceutical Excipients, 2nd ed. (1994).

The polyethylene glycol glyceryl esters useful herein are selected from those containing about 30 to about 35 oxyethylene groups. Polyethylene glycol 32 glyceryl
20 ester sold as "GELUCIRE 50/13" by Gattefosse S.A. of France is a preferred ester. Mixtures are operable.

The amounts of ingredients used in the compositions are generally within those shown in the following table.

	Broad range	Narrow range	Preferred range
Bio-affecting agent(s)	1 - 50%	5 - 40%	20 - 30%
PEG	0 - 90%	60 - 90%	60 - 80%
Glyceryl ester	0 - 60%	1 - 10%	2.5 - 7.5%
Excipient(s)	0 - 98%	10 - 50%	10 - 30%

II. Processes

Useful processes for making the microparticles of the invention include liquiflash

5 conditions as well as other thermoforming processes known in the art, eg., extrusion.

"Liquiflash conditions" are generally those under which the material, called a feedstock, is rapidly heated just to the point at which it undergoes intraparticulate flow and partially deforms or liquifies so that it can pass through openings in a suitable spinning device.

10 The passage of the liquiflash particles through openings is in response to centrifugal forces within the spinning head, which forces "expel" the particles, as discrete solids out of the device and into the atmosphere. The expelled materials instantly reform into particles, without the application of external shaping forces, which particles have different morphologies from those of the feedstocks.

Applicants have found that one particular spinning device is highly useful in
 15 making the microspheres of the invention. In U.S. Patent 5,458,823, a spinning device is described which uses a spinning head including a base and a cover. A plurality of closely spaced heating elements are positioned between the base and cover, forming a barrier through which the material to be processed passes. In use, the head rotates and the heating elements are heated to temperatures that bring about liquiflash conditions in the
 20 materials being processed. As the spinning head rotates, the centrifugal force created by its rotation expels the material through spaces between the heating elements. The material forms discrete, generally spherical particles as it exits.

The production of microspheres for use in the subject invention may be optimized by the use of a V-groove insert inside the spinner head. The insert is described in pending U.S. Patent Application Serial No. 08/874,515, filed June 13, 1997. The insert has grooves therein, which grooves have a uniform depth and width through their length, so that highly uniform discrete microspheres or other particles are produced. Using this or a similar insert, the spinning device is operated at 50 to 75 Hz, at about 10 to 25% power, and at temperatures which yield liquiflash conditions.

It should be noted that "liquiflash conditions" vary with the properties of the material, or feedstock, being processed. Since the feedstocks contain many substances in varying amounts, the parameters need to yield "liquiflash conditions" for a particular mixture must be ascertained by processing small quantities or samples before processing large ones. Typically, the feedstocks contain active agent(s) and processing aids.

Among the co-assigned patents and patent applications which describe the preparations of microspheres containing bio-affecting agents re: U.S. 5,458,823; U.S. 5,638,720; and U.S. SN. 08/874,215, filed June 13, 1997.

III. Microparticles

While particulates made using various thermoprocessing technologies are useful, microspheres described below are preferred.

The microspheres or other particulates are generally solid spherical bodies of about 150 to about 250 microns mean particle diameter.

It is preferred that they be produced via a direct spheronization process, such as liquiflash or other suitable techniques. However, they may be made by physically

altering the size and/or shape of non-spherical particles by extrusion/spheronization or melt granulation processes.

When microspheres are made by direct spheronization of compositions containing active agent(s), the fatty esters and optional emulsifiers/surfactants, the fatty esters
5 function as spheronization aids.

The microspheres may be used as is, i.e., in powder or sachet products for delivering active agents. Alternatively, they may be used in the production of solid, liquid (suspensions), or semi-solid (e.g., gel-like) comestible units, etc. Tablets and capsules are preferred.

10 It is preferred that the microspheres of the invention be used in combination with excipients which have been formed into floss or matrix particles. Useful flosses are generally made from saccharide based carriers. See U.S. patents 5,622,719 and 5,587,172.

Once the floss and microsphere ingredients are combined, they can be shaped into
15 comestible units.

IV. Coatings

One or both of the microspheres and the dosage units can be coated or encapsulated with at least one coating. Useful coating formulations contain polymeric
20 ingredients as well as excipients conventionally employed in such coatings. The coatings are generally used for such purposes as taste-masking, controlling release and the like.

Useful taste-masking coatings can include (meth)acrylate/cellulosic polymers. Ethylcellulose (EC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose

(HPMC), and polymethacrylate polymers, such as Eudragit RS, Eudragit RL or mixtures thereof are useful. Preferred combinations include EC/HPC and Eudragit RS/Eudragit RL.

Controlled release coatings generally contain at least one of: ethylcellulose (EC),
5 hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC),
hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, and the like. The
"Eudragits" designated as NE 300, RS, L 30 D, are useful. Mixtures are operable.

Coating levels of about 0 to about 150% are effective, with levels of about 5% to
about 30% being preferred.

10 Coating devices include those conventionally used in pharmaceutical processing,
with fluidized bed coating devices being preferred.

Examples

Examples I through IIC show the preparation of microspheres.

15 Example I

Microspheres were made from a composition containing:

Famotidine	30%
PEG 4600	65%
Gelucire 50/13	5%

20 The spheres were made by the following procedure:

The PEG 4600 and Gelucire 50/13 were milled through a 40 mesh screen using a
Fitzmill M5A. The milled ingredients and famotidine were blended in a high shear mixer
for 3-10 minutes. The mix was processed into spheres via spinning using the 5" V-

grooved head spinning device (at 65 Hz speed and 27.5% duty cycle) disclosed in U.S.

SN. 08/874,215, file June 13, 1997.

The microspheres were collected and sieved through a #40 mesh onto #140 mesh.

Examples IIA, IIB, and IIC

5 Using procedures similar to those of Example I, microspheres are made from compositions containing:

	<u>A</u>	<u>B</u>	<u>C</u>
Lovastatin	40%	40%	30%
PEG 4600	60%	0%	65%
10 Gelucire 50/13	0%	60%	5%

The microspheres are collected and used to produce capsules.

Examples III and IV illustrate coating procedures.

15 Example III

Microspheres from Example I were coated with a coating solution, consisting of a 3:7 combination of Eudragit RS/Eudragit RL along with PEG 4000 as a plasticizer and talc as an anti-adherent, at 30% coating level by weight, using a Glatt GPCG-60 fluid bed coater. The coated microspheres were used to make FLASH DOSE tablets, as described
20 in Example V, below.

Example IV

The microspheres of Example I were coated with a 45:55 EC/HPC polymer solution at 30% coating level by weight using an MP Niro-1 fluid bed coater.

Example V

25 This example shows the preparation of tablets.

The following ingredients were blended in a Littleford FKM 600 blender for 10 to 15 minutes:

	Coated famotidine microspheres (Example III)	38.52 %
	0.5% ethanol treated floss*	58.53 %
5	Mint flavor	2.00 %
	Syloid 244 P	0.25 %
	Sodium stearyl fumarate	0.50 %
	Acesulfame potassium	0.20%

* The floss particles contained 78.25% sucrose, 11.0% sorbitol, 10.0% xylitol and 0.75% TWEEN and were made using the procedure in Example IIIB of U.S. SN. 08/915,968, filed August 20, 1997. They were then sprayed with 0.5% ethanol by weight and dried.

The ingredients were mixed and compressed on a Kilian rotary press using 9mm flat faced radial edge tooling to a tablet weight of 225.0 mg, 1.0 lb. hardness, equivalent to 20 mg famotidine dose; or using 12mm flat faced radial edge tooling to a tablet weight of 450 mg, 1.0-1.5 lb hardness, equivalent to 40 mg famotidine dose.

Comestible Units

The microparticles of the invention can be used in the preparation of comestible units for delivery via a variety of routes, including oral, transdermal, nasal, topical, buccal, anal and the like. Solid, liquid and semi-solid products can be made.

Tablets and capsules are preferred dosage forms.

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

We claim:

- 5 1. A composition useful in the production of thermoformed microparticles comprising:
- (a) about 10% to about 50% of at least one bio-affecting agent, and
 - (b) about 50% to about 90% of at least one processing aid selected from the group consisting of (i) a high molecular weight polyethylene glycol and (ii) a polyethylene glycol glyceryl ester.
- 10 2. The composition of claim 1 wherein (b) contains both (i) and (ii).
3. The composition of claim 2 wherein the microparticles are microspheres and the bio-affecting agent is famotidine or lovastatin.
- 15 4. A process for producing microparticles comprising the steps:
- (1) mixing at least one bioaffecting agent with at least one processing aid selected from the group consisting of: (i) a high molecular weight polyethylene glycol and (ii) a polyethylene glycol glyceryl ester;
 - 20 (2) subjecting the mixture of step (1) to thermoforming conditions to produce microparticles; and
 - (3) recovering the microparticles of step (2).
5. The process of claim 4 wherein the processing aid contains both (i) and (ii).

25

6. The process of claim 5, including the added step of coating the microparticles of step (3).

7. The process of claim 6 wherein the microparticles are microspheres and the
5 bioaffecting agent is famotidine or lovastatin.

8. Microparticles produced using the process of claim 5.

9. Microparticles produced using the process of claim 6.

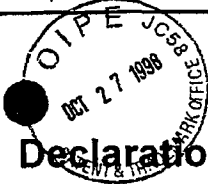
10. A comestible unit containing the microparticles of claim 9.

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Abstract of the Disclosure

5 Microparticles containing bioaffecting agents can be made via thermoforming techniques in the presence of one or more processing aids. The microparticles have generally consistent shape, size and release/taste properties.

04170926-102748
942201-9267160



Docket No.
0051

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

BIOAFFECTING MICROPARTICLES

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International

Application Number _____

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

None

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

_____	_____
(Application Serial No.)	(Filing Date)
_____	_____
(Application Serial No.)	(Filing Date)
_____	_____
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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